MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2025.2.354.361

Assessment of Serum Magnesium Level in Migraine Patients in a Tertiary Care Hospital

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ABSTRACT

Increased irritability of the brain is considered as a cause of migraine. Factors like low serum magnesium levels and mitochondrial abnormalities are responsible for increased irritability of the brain and touted to be responsible for pathophysiology of migraine. The primary aim of the study is to estimate the serum magnesium level and conduct Event related Potential (ERP) study in migraine subjects and also to find out the association between serum magnesium level and the cognitive function. This study was conducted in 50 clinically diagnosed migraine subjects in the age group of 18-40 years of both genders and 50 age matched controls of both genders from a similar background were selected for the study. Subjects with a minimum of two years of migraine history were selected for the study from the Neurology outpatient department, Stanley Medical College, Chennai, Tamilnadu, India. After eliciting detailed history, General and Clinical examination was done. Cognitive function was assessed using Event related Potential (ERP) study. Serum magnesium level was estimated using Calmagite Dye method by automated analyzer EM-360. Serum magnesium level was found to be lower in migraine patients compared to healthy controls. This present study shows that there was a significant cognitive impairment in migraine subjects when compared to the control group reflected by Cognitive Evoked potential study. Migraine subjects also have low serum Magnesium level than the control group. The serum magnesium levels were inversely related to the latency in Cognitive Evoked Potential which suggests cognitive impairment in migraine subjects when compared to the control group.

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Key Words
Migraine, cognition, serum magnesium

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Received: 31 December 2024
Accepted: 15 January 2025
Published: 29 January 2025

Citation: Dr. V. Rajalakshmi, Dr. R. Anbarasi, Dr. K. Saravanan and Dr. R. Venkatesan, 2025. Assessment of Serum Magnesium Level in Migraine Patients in a Tertiary Care Hospital. Res. J. Med. Sci., 19: 354-361, doi: 10.36478/makrjms.2025.2.354.361

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INTRODUCTION

Migraine is a chronic neurovascular disorder and is the second most common cause of headache. Migraine is one of the most frequent headache related and neurologic cause of disability in the world. The estimated prevalence of a Migraine was approximately 15% among women and 6% among men over a one year period. Migraine is characterized by an episodic headache, precipitated often by disturbances like sound, movement, sensitivity to light and is often associated with nausea and vomiting. Migraine is a recurrent primary headache disorder affecting both neuronal and cerebrovascular systems[1]. Migraine is associated with functional alteration which has both physical and emotional ramifications. Migraine is a chronic disorder causing interruption of cortical and subcortical circuit which may eventually lead to impairment of cognitive activity[2]. Increased irritability of the brain is considered as a cause of migraine. Factors like low serum magnesium levels and mitochondrial abnormalities are responsible for increased irritability of the brain[3-5]. In addition, low serum magnesium level has been considered as a cause for cognitive decline[6]. Level of cognitive functioning in migraine patients must be taken into consideration before planning self-care and it has to be modified according to the subjects capability and needs. This study intends to find the serum magnesium level in migraine patients and also the association between serum magnesium level and cognition.

Review of Literature: Migraine is a chronic neurological disorder[7]. It is characterized by attacks of headache, hypersensitivity to visual, auditory, olfactory and cutaneous stimuli, nausea and vomiting[8]. Headache classification subcommittee of the international headache society defined migraine as "common neurologic syndrome the typical features of which include a moderate to severe, recurrent, unilateral or bilateral, throbbing headache lasting hours to days, which is commonly accompanied by nausea, photo phobia and phono phobia and worsened by routine physical exertion"[9]. Magnesium is the eighth most common element in the crust of the earth and fourth most abundant mineral in human body. Humans should include magnesium in their diet in order to prevent magnesium deficiency[10].

Distribution of Magnesium in the Body: The normal adult human body contains 20-28 grams of magnesium. Magnesium is mainly an intracellular cation, with <1% percent in extracellular fluids. Approximately, 53% is in bones, 27% is in muscles and 19 % is in other soft tissues.

Recommended Dietary Allowance:

- Adult males 400-420 mg/day.
- Adult females 310- 320 mg/day.

Functions of Magnesium:

- Grober U *et al.* listed out the following as the functions of magnesium[10].
- Magnesium is involved in >300 essential metabolic reactions (e.g., all Adenosine Triphosphate (ATP)-dependent reactions).
- Energy production (ATP production).
- Enzyme activation (examples).
- Mitochondrial ATP syntheses, Na+/K+-ATPase, Creatine kinase, Hexokinase, Hexokin, Phosphofructokinase, Hexokin tyrosine kinase activity of the insulin receptor.
- Membrane function.
- Transmembrane electrolyte flow, active transport of potassium and calcium through the cell membrane, regulation of cell adhesion and cell migration.
- Structural roles.
- Component of mineralized bone, multiple enzyme complexes, mitochondria, proteins, polyribosomes and nucleic acids.
- Calcium antagonist/NMDA-receptor antagonist.
- Control of calcium inflow at the cell membrane (during the course of contractions and regulation of vascular muscle tone), muscle contraction/ relaxation, action potential conduction in nodal tissue, neurotransmitter release, neuromuscular impulse conduction (inhibition of calcium-dependent acetylcholine release at the motor end plate), maintenance and stabilization of membrane physiology.
- Breakdown and energetic utilization of carbohydrates, proteins and fats in intermediate metabolism (e.g., glycolysis, respiratory chain phosphorylation). Primarily ATP exists as a complex with magnesium (MgATP).

Migraine and Hypomagnesemia: There are two theories linking migraine and magnesium.

- Stress leads to increased excretion of magnesium producing a hypomagnesemia state which finally triggers migraine.
- Migraine sufferers excrete excess magnesium due to stress resulting in transient serum hypomagnesemia.
- Various studies had demonstrated decreased magnesium in cerebrospinal fluid during migraine attacks. Similarly studies had reported decreased serum magnesium levels and salivary magnesium levels during migraine attacks[11].

- Role of Magnesium in Migraine Pathophysiology
- Brain hyper excitability caused by low magnesium levels, mitochondrial abnormalities with abnormal phosphorylation of adenosine 5'-diphosphate, a dysfunction related to nitric oxide, or calcium channelopathy[3-5].
- Reduced level of Magnesium leads to mitochondrial oxidative phosphorylation disorder and neuronal polarization instability which is characteristic of Migraine.
- Reducing magnesium levels can lead to calcium channel opening that increases intracellular calcium, glutamate release and increased extracellular potassium which finally causes depression of the brain[4].
- The NMDA receptors play an important role in the initiation and spreading of cortical depression. Magnesium could act as antagonist against NMDA receptor complex. Studies had shown that magnesium could block the cortical depression induced by glutamate[12].
- Calcium gene related peptide (CGRP), a neuropeptide whose levels were found to be increased before an impending migraine attack and the levels returned to normal after the attack. Magnesium levels were found to have effect on the circulating levels of CGRP.
- Another mechanism of migraine involves Nitric oxide and its derivatives acting on NMDA receptors, as already told Magnesium is an antagonist to NMDA receptor complex.

Magnesium and Cognition: Magnesium plays a most important role in neurochemical transmission and its deficiency related to cognitive impairment. Basheer MP *et al.* reported that Magnesium was significantly related to the cognitive impairment[6]. Mancoyo R reported that magnesium supplementation could correct acquired mild cognitive defects in infants[13]. Magnesium protected learning and memory functions in Alzheimer model rats[14]. Corsonello A in their study reported that there was significant association between magnesium imbalance and cognitive impairment[15]. The present study was conducted to evaluate the cognitive functions in migraine subjects and to find out whether the cognitive function is associated with serum magnesium levels.

MATERIALS AND METHODS

This study was conducted in 50 clinically diagnosed migraine subjects in the age group of 18-40 years of both genders and 50 age matched controls of both genders from a similar background were selected for the study. Subjects with a minimum of two years of migraine history were selected for the study from the Neurology outpatient department, Stanley Medical College, Chennai, Tamilnadu, India. The study protocol was presented before the institutional ethical committee for approval and got approved. Individual informed consent was obtained from the participants. The confidentiality of the data collected was strictly ensured by electronic storage. After eliciting detailed history, General and Clinical examination was done. Cognitive function was assessed using Event related Potential (ERP) Study. Serum magnesium level was estimated using Calmagite Dye method by automated analyzer EM-360.

Study Design: Case-control study.

Duration of Study: July 2017 to July 2018.

Subject Selection:
Inclusion Criteria: The study population consisted of 50 Migraine subjects and 50 healthy controls.

Migraine Subjects: Clinically diagnosed migraine subjects were recruited from the Neurology outpatient department at Govt. Stanley Medical College Hospital, Chennai. 50 clinically diagnosed Migraine subjects were selected in the age group of 18-40 years of both gender. Migraine subjects with a minimum of two years duration were selected for the study based on International classification of Headache Disorders 3 (ICHD)-International headache society 2013[16]. Study was conducted in migraine free period.

Control Group: The Control group was recruited from the Master Health Checkup, in Stanley medical college and Hospital and the accompanying persons who volunteered for the study. They were age and gender matched and had similar educational qualification and socioeconomic background.

Exclusion Criteria:
- Any other type of head ache.
- Neurological disorders.
- Psychiatric illness.
- Auditory dysfunction.
- H/O Head injury affecting auditory functions/ central nervous system.
- Diabetes mellitus.
- Hypertension.
- Thyroid disorders.
- H/O Chronic treatment for any other chronic illness.
- H/O Smoking.
- Chronic Alcoholism.
- Drug abuse.
- On oral contraception.

All the subjects were explained about the nature and procedures involved in this study. Their consent was obtained.

History Taking: The demographic details were obtained. Duration of disease, type and nature of headache, duration of headache, number of episodes per day/week/month, other associated symptoms and treatment history were recorded. Details regarding the precipitating factors were also recorded.

Clinical Examination: Height and weight were measured and Body mass index, respiratory rate and temperature were recorded. General and systemic examination was done. Complete examination of external ear was done for both ears and pure tone audiometry was done to rule out any auditory impairment in the ENT department, Stanley Medical College Hospital.

Assessment of Cognition:

Cognitive Evoked Potential Study: Cognitive evoked potential study was done for all the study subjects.

Equipment: The Cognitive Evoked Potential was recorded using a computerized recorder-RMS EMG EP MARK II (Recorders and Medicare Systems Pvt. Ltd., Chandigarh. The machine includes a stimulator, recording electrodes, filter, amplifier, signal 90 verge, electrical safety.

Stimulator: The auditory stimulus in the form of clicks was given to both ears via transducers placed in the headphone.

Recording Electrodes: Surface silver/silver chloride disc electrodes are used for recording the potentials.

Filter: Filter is a device, which selectively restricts a particular frequency domain. The filter band is the frequency range, which is transmitted through the filter. The frequency range which is rejected is known as stop band. Filtering is necessary for eliminating the noise and optimizing the electro physiological recording. Filtering also brings out the characteristics of the wave form. The low frequency filters removes the low frequency components and allows higher frequencies to pass the filter and are called high pass filters. Similarly the high frequency filter removes the higher frequencies and allows only the low frequency they are also known as low pass filters.

Filter Setting for Cognitive Evoked Potential Recording is as Follows:

Low pass filter	30-100 Hz
High pass filter	0.3-1Hz

Amplifiers: ERPs are small, relative to the spontaneous brain activity, i.e., they have a low signal to noise ratio. Since the biological signals are very small, they need to be amplified. Cognitive evoked potentials are usually amplified 10,000 times.

Signal Averager: To increase the signal to noise ratio, ERP averaging is done. To separate the cognitive evoked responses from the background EEG signal, averaging is done. This is based on the fact that the evoked potential electrical activity is time specific, whereas the random electrical activity is not time specific.

Preparation of the Individuals: The individuals were instructed to have a shampoo bath on the day of recording and were advised not to use hair spray or oil. The subjects were instructed to avoid beverages and strenuous exercises on the day of recording. They were taken to a silent room in neurophysiology laboratory, and made to sit down comfortably in a chair with eyes closed.

Electrode Placement: The electrode placement sites were cleaned with spirit and cotton. The gold plated copper disc electrodes were used for recording. Surface electrode recordings were desirable because they are painless, have better stability and little chances of infection. 1 cm disc electrodes filled with conducting paste were used. Electrode paste was used to reduce the impedance below 5 kilo ohms. Impedance was checked and was <5 kilo ohms. The electrodes were placed according to 10-20 International system[17].

- Active surface recording electrode was placed on Vertex-Cz.
- Two linked reference electrodes, one on each mastoid (A1 and A2) with a jumper electrode.
- Ground electrode was placed over the forehead.

Recording the Cognitive Evoked Potential: Recording was done in Neurophysiology Laboratory of Research Wing, Department of Physiology, Stanley Medical College. The laboratory temperature was maintained uniformly. The recordings were done in the forenoon between 10 am to 12 noon in sitting posture two hours after a light breakfast. The subject was asked to recline on a chair comfortably with their feet placed on wooden board. The cognitive evoked potential was recorded by using the standard auditory odd ball paradigm. Random sequences of two distinguishable auditory clicks were delivered binaurally. It includes frequent stimuli (80%) of 1 KHz frequency and rare stimuli (20%) of 2 KHz frequency. The individuals were asked to raise their finger on hearing the rare stimuli. The intensity of the stimuli was 60 db above the

hearing level. The stimuli were presented at a frequency of 1 per second, each lasting for 100 milliseconds. The responses were filtered with a band pass filter of 0.3-30 Hz., the responses were amplified 10,000 times and averaged for 40 responses. The individuals were asked to fix their eyes on a particular point on the wall during recording to avoid electro oculographic artifacts.

Parameters Studied: The waves were then computed separately for rare and frequent stimuli, the latency of the N 100, P 200, N 200 and P 300 waves and P 300 wave amplitude of the rare stimuli were noted down.

Serum Magnesium Level: Serum Magnesium level was estimated using Calmagite Dye method by automated analyzer EM-360 in the Department of Biochemistry, Stanley medical college and hospital with prior permission from the Head of the Department.

Sample Collection and Preparation: About 5ml of random blood sample was collected from each individual participated in the study under aseptic precautions in plain toped venipuncture tubes without any anticoagulants or gel barrier. After the collection of 30 minutes, samples were centrifuged at 2000-2500 rpm for 10 minutes. Samples were separated immediately and stored at -20° C.

Principle: Magnesium combines with Calmagite in an alkaline medium to form a blue colored background. Interference of Calcium and proteins is eliminated by the addition of specific chelating agents and detergents. Intensity of the color formed is directly proportional to the amount of magnesium present in the sample.

Alkaline Medium:

Mg+Calmagite ---------->Colored complex.

Reagent Composition

Contents	25ml	75ml
L1: Buffer	12.5ml	37.5ml
L2: Color Reagent	12.5ml	37.5ml
S: Magnesium Standard (2.0mEq/L)	2 ml	2ml

System Parameters:

- **Reaction:** End Point.
- **Wavelength:** 510nm.
- **Zero Setting:** Reagent Blank.
- **Incubation Temp:** R.T.
- **Incubation Time:** 5min.
- **Sample Volume:** 0.01 ml.
- **Reagent Volume:** 1.00 ml.
- **Standard:** 2.0mEq/L.
- **Reaction Slope:** Increasing.
- **Linearity:** 10mEq/L.
- **Units:** mEq/L.

Procedure:

- **Wavelength/Filter:** 510nm (Hg 546nm)/Green.
- **Temperature:** R.T.
- **Light Path:** 1cm.

The following were pipetted into clean dry test tubes labeled as (B), Standard (S) and Test (T).

Addition Sequence	B (ml)	S (ml)	T (ml)
Buffer Reagent L1	0.5	0.5	0.5
Color Reagent L2	0.5	0.5	0.5
Distilled Water	0.01	-	-
Magnesium Standard (S)	-	0.01	-
Sample	-	-	-

They were mixed well and incubated at room temperature (25°c for 5 minutes). The absorbance was measured for the standard and test sample against the blank within 30 minutes.

Reference Values of Magnesium:

- **Serum Magnesium Level in Children:** 1.5-2.0mEq/L.
- **Serum Magnesium Level in Adult:** 1.3- 2.5mEq/L.
- **CSF Magnesium Level:** 2.0-3.0mEq/L.
- **Urine Magnesium Level:** 6.0-8.5mEq/L.

Statistical Analysis: Statistical package for Social Sciences (SPSS) version 20.0 was used for statistical analysis. The results were expressed as mean±standard deviation and independent t test. The correlation was tested by Pearson's correlation. The difference was considered significant when $p<0.05$.

RESULTS AND DISCUSSIONS

Table 1: Distribution of Study Participants According to Age

Groups	Mean	SD	p-value
Migraine	31.00	6.698	>0.05
Control	30.18	6.524	

The mean age of the Migraine subjects was 31±6.69 years and that of control group was 30.18±6.52 years. The difference is statistically insignificant, thus controls are age matched with cases.

Table 2: Distribution of Study Participants According to Sex

	Cases		Control	
Sex	N	%	N	%
Male	3	6	6	12
Female	47	94	44	91
Total	50	100	50	100

Table 3: Distribution of Migraine Subjects According to Duration

Duration (Years)	No of Persons	Percent (%)
2	13	26.0
3	16	32.0
4	5	10.0
5	7	14.0
6	3	6.0
8	2	4.0
10	4	8.0
Total	50	100.0

The mean duration of migraine subjects was 4.06±2.31 years.

Table 4: Distribution of Study Participants According to Height, Weight and BMI

Characteristic	Cases	Control
Height (Cm)	155.72±4.18	159.4±4.09
Weight (Kg)	58.38±8.84	59.52±8.63
BMI (Kg/m^2)	24.12±3.78	23.37±2.71

Table 5: Comparison of Mean Value of Serum Magnesium Levels Between Migraine and Control Group

Groups	Mean	SD	p-value
Migraine	1.57	0.41	<0.05
Control	2.07	0.29	

The Serum Magnesium levels were found to be low in Migraine subjects than the Control group and the difference was found to be statistically significant.

Table 6: Correlation Between Target N100 Wave Latency and Serum Magnesium Level

	Serum Magnesium Level	
Target N100 wave Latency	**r-value**	**p-value**
	-0.350	<0.05

For every unit decrease in Serum Magnesium in Migraine subjects, the Target N100 wave Latency was prolonged by 0.350 units. The correlation was statistically significant.

Table 7: Correlation Between Target P200 wave Latency and Serum Magnesium Level

	Serum Magnesium Level	
Target N200 wave Latency	**r-value**	**p-value**
	-0.436	<0.05

For every unit decrease in Serum Magnesium in Migraine subjects, the Target P200 wave Latency was prolonged by 0.436 units. The correlation was statistically significant.

Table 8: Correlation Between Target N200 wave Latency and Serum Magnesium Level

	Serum Magnesium Level	
Target N200 wave Latency	**r-value**	**p-value**
	-0.400	<0.05

For every unit decrease in Serum Magnesium in Migraine subjects, the Target N200 wave Latency was prolonged by 0.400 units. The correlation was statistically significant.

For every unit decrease in Serum Magnesium in Migraine subjects, the Target P300 wave latency increased by 0.047 units. The correlation was not statistically significant.

Table 9: Correlation Between Serum Magnesium and Target P300 Wave Latency

	Serum Magnesium Level	
Target P300 wave Latency	**r-value**	**p-value**
	-0.047	<0.05

Basic Characteristics of the Study Groups: The study groups included 50 Migraine subjects and 50 healthy controls. The mean age of the migraine subjects was 31±6.69 years and that of the control was 30.18±6.52 years (Table 1). 94% of the cases were females and 91% of the controls were females (Table 2). Both the cases and control groups were similar with respect to both age and gender. The mean duration of migraine was found to be 4.06±2.31 years (Table 3).

Serum Magnesium Levels Between the Migraine and the Control Group: The mean serum magnesium level (mEq/L) of the study participants with Migraine was 1.57±0.41 and that of the controls was 2.07±0.29 (Table 5). The observed difference was found to be statistically significant. Serum Magnesium levels among the migraine subjects were found to be less than that of healthy controls. Samaie *et al.* reported a similar decrease in the Serum Magnesium levels among the Migraine subjects than controls[5]. Huang *et al* in their study also reported a similar reduction in Serum Magnesium levels in the Migraine subjects[18]. Gallai V *et al.* reported low serum magnesium levels in the Migraine subjects than the normal persons and also observed that the level declined further during the phase of a migraine attack. Talebi M in his study also reported a similar finding[4]. In contrary to the findings of the current study, Azzarzadegan *et al.* reported that there was no difference in the serum magnesium levels between the Migraine subjects and the control group[19]. Similar observation was reported by schoenen[20].

Correlation Between Serum Magnesium Levels and Target N100, P200, N200 and P300 Wave Latency: This study shows negative correlation between the serum magnesium level and target N100, P200 and N200 wave latency. With every unit decrease in serum magnesium level among the Migraine subjects, the N100 wave latency was increased by 0.350 units (Table 6), the P200 wave latency was also increased by 0.436 units (Table 7) and the N200 wave latency was increased by 0.400 units (Table 8). The correlation between the serum magnesium level and the target

N100, P200 and N200 wave latency were found to be statistically significant. Similarly for every unit decrease in serum magnesium level among the migraine subjects, the P300 wave latency was also prolonged by 0.047 units (Table 9), but the result was not significant. With the above findings, there was a significant association between the low serum magnesium level and the cognitive impairment in this study. Magnesium plays a most important role in neurochemical transmission and its deficiency related to cognitive impairment. Basheer MP *et al.* reported that magnesium was significantly related to the cognitive impairment[6]. Magnesium deficiency may affect the cognitive performance in elderly individuals[21]. Cillier AE *et al* reported that low serum magnesium levels were significantly associated with the cognitive decline[22]. Mancoyo R reported that magnesium supplementation could correct acquired mild cognitive defects in infants[13]. Magnesium protected learning and memory functions in Alzheimer model rats[14]. Corsonello A in their study reported that there was significant association between magnesium imbalance and cognitive impairment[15]. This present study shows that there was a significant cognitive impairment in migraine subjects when compared to the control group reflected by Cognitive Evoked potential study. Migraine subjects also have low serum Magnesium level than the control group. The serum magnesium levels were inversely related to the latency in Cognitive Evoked Potential which suggests cognitive impairment in migraine subjects when compared to the control group.

CONCLUSION

- There is significant cognitive impairment in migraine subjects as evidenced by Cognitive Evoked Potential study.
- This study also adds strength to the fact that magnesium would play a role in the pathogenesis of migraine, as migraine subjects have low serum magnesium level than that of the control group.
- Present study also shows that low serum magnesium levels were associated with cognitive impairment as indicated by prolonged latency in Cognitive Evoked Potential in migraine subjects.
- Further studies can be done to establish the causal relationship if any, between the serum magnesium and migraine.
- Also Randomized control trials can be done with magnesium supplementation to find out the benefits in migraine subjects.
- Hence, in migraine subjects Cognitive Evoked potential study and serum magnesium level estimation can be recommended to assess the cognitive impairment, so that the suitable intervention can be planned to improve their quality of life.

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